Comparison of spheno-occipital synchondrosis closure, cervical vertebrae maturation and hand-wrist maturation as skeletal maturation indicators

A Thesis submitted to the faculty of the graduate school of the University of Minnesota
By

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In partial fulfillment of the requirements for the degree of Master of Science

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June 2018

I would like to dedicate this thesis to my parents.
Thank you for everything.

Acknowledgements

I would like to acknowledge and thank everyone who has supported me throughout my education and journey of becoming an orthodontist. My parents, Kevin and Kathy, provided me with all the resources to make my dreams come true and for that I will always be grateful. My fiancé and partner of over 11 years, Kevin, has been by my side through all the ups and downs college, dental school and orthodontic residency brings. My co-residents Rachel, Olga, Dustin, Amy and Hani have made residency so enjoyable and have become lifelong friends. I would also like to thank the rest of my friends and family who have contributed to my happiness and success. I have the most unbelievable support system and I would not be where I am today without it.

I would like to thank all the faculty and staff in The University of Minnesota's Division of Orthodontics. Every single person has made a profound impact on my education and development of clinical skills. Both statisticians, Lei Zhang and Ashley Peterson, helped immensely with my thesis statistics and I thank them for all they did. Dwight Anderson and his hard work was crucial for the preparation and data collection for my thesis. I would like to thank Dr. Brent Larson and Dr. John Beyer for serving on my thesis committee. Lastly, I would like to acknowledge and thank Dr. Mansur Ahmad, who was the primary advisor for my thesis. He not only provided me with crucial guidance throughout this project but has gone above and beyond to mentor me throughout dental school and orthodontic residency.

Abstract

Aim: To examine the correlation between three skeletal maturation indicators: hand-wrist maturation, cervical vertebrae maturation and the spheno-occipital synchondrosis closure.

Methods: The hand-wrist radiographs and images of cervical vertebrae and the spheno-occipital synchondrosis (extracted from CBCTs) of 61 patients were graded for skeletal maturation by three raters on two different dates. Their stages were compared to analyze the agreement between the three skeletal maturation markers. The reliability of the staging of the three analyses was also studied.

Results: The hand-wrist maturation analysis had the highest intra-rater (κ= 0.895) and inter-rater reliability (Kendall's coefficient = 0.972), while the spheno-occipital's reliability was the lowest (intra-rater reliability κ = 0.642; inter-rater reliability Kendall's coefficient = 0.886). The skeletal maturation indicators that agreed most closely were the hand-wrist maturation and the spheno-occipital synchondrosis (κ = 0.5079).

Conclusions: The three skeletal maturation analyses studied are related but not inter-changeable. More clear definitions of the staging of the analyses and calibrations of the analyses are needed to improve reliability. A clinician should rely on multiple markers to make decisions regarding a patient's growth potential.

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Introduction

One of the greatest challenges facing orthodontists is deciding when it is the ideal time to treat a patient. When diagnosing and treatment planning an orthodontic case, it is of utmost importance for the orthodontist to have knowledge of a patient's growth status and potential. Knowing if a patient is pre-pubertal, at their peak pubertal growth or post-pubertal growth can dictate what treatment modalities and timing are best, so the patient can have the ideal treatment outcome. Pubertal growth spurts are effected by many factors and therefore chronological age is not always a reliable indicator (Fishman 1982). Skeletal age is more reliable than chronological age, especially for those children who are advanced or delayed.

For effective growth modification, understanding the amount of growth potential remaining is crucial. For example, the ideal times for palatal expansion, a functional appliance or an orthognathic surgery, are not at the same chronological age for every patient. For growth modification of the maxilla (i.e. expansion with a rapid palatal expander, headgear, or protraction face mask), treatment should be initiated prior to the peak pubertal growth spurt (Soegiharto, Cunningham, and Moles 2008; Franchi, Baccetti, and McNamara 2004). Whereas, growth modification of the mandible is thought to be most effective during peak growth rather than before (Baccetti, Franchi, and McNamara 2002). Furthermore, most types of orthognathic surgery and implant placement surgery are best done once growth is complete (McNamara and Franchi 2018).

Over the years many studies have focused on finding a skeletal maturation marker that correlates to peak skeletal growth. Parameters such as standing height, pubertal markers (initiation of menstrual cycles, secondary sex characteristics, voice changes, etc.), chronological age, radiographic assessments of skeletal landmarks and dental development, have been used to assess growth.

Historically, many orthodontists have based their determination of growth potential by examining either a hand-wrist radiograph or observing the cervical vertebrae maturation (CVM) as seen on the lateral cephalometric radiograph. With the increase in use of cone beam computed tomography (CBCT) by orthodontists, there has been more focus on the spheno-occipital synchondrosis maturation. The spheno-occipital synchondrosis can be easily visualized on CBCT images and its closure is believed to correlate closely with the maturation of the jaws (Enlow 1990).

This study focuses on three radiographic assessments of bone maturation methods: hand-wrist maturation, cervical vertebrae maturation and the closure of the spheno-occipital synchondrosis.

Literature Review

Hand-Wrist Maturation

Gruelich and Pyle developed an atlas based on the hand-wrist radiographs of upper class white girls and boys from 1931-1942 (Greulich and Pyle 1959). This atlas is comprised of radiographic images of references for each stage of the hand-wrist development for both females and males age birth to 19 years old. Leonard Fishman developed the System of Skeletal Maturation Assessment (SMA) in 1982 to evaluate hand-wrist radiographs (Fishman 1982). This assessment focused on six anatomical positions on the hand wrist: thumb, third finger (distal, middle and proximal phalanx), fifth finger (middle phalanx) and radius. Four stages of bone maturation were looked at: widening of the epiphyseal plates in phalanxes, ossification of the sesamoid bone, capping of the epiphyseal plates and fusion of the epiphysis with the diaphysis. Fishman analyzed the maturation of these sites and created eleven stages of Skeletal Maturation Indicators (SMIs) (Figure 1). He reported average ages for each stage of maturation in females and males. It was concluded that mandibular and maxillary growth demonstrate a close association with skeletal maturation, but both do achieve their maximum growth rate later than statural growth. Fishman believed that due to the wide variability in skeletal maturation, chronological age alone is not enough to determine peak growth (Fishman 1982).

Fishman

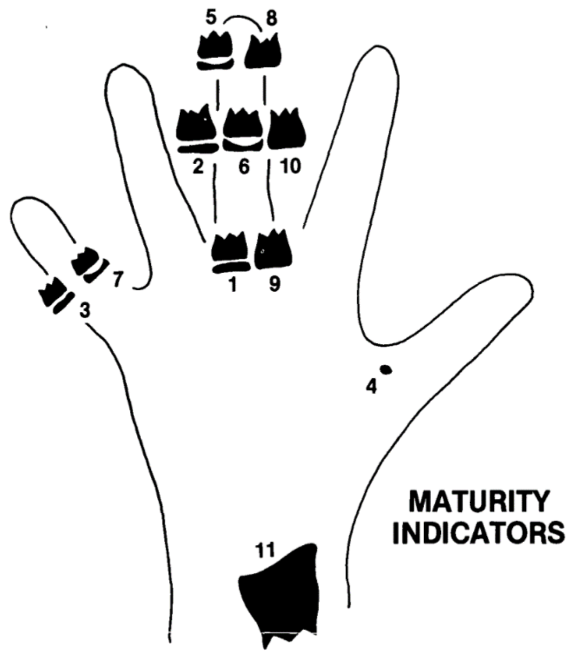


Figure 1: Schematic illustrating Fishman's 11 SMIs of the hand-wrist

The hand-wrist radiograph has been proven to be very accurate and studied by many researchers (Fishman 1982; Hagg and Taranger 1982; Bjork and Helm 1967). It is widely accepted that the maturation of the hand-wrist bones is well correlated with statural growth, but its correlation to craniofacial growth has been questioned. Verma et al. concluded that there was no significant correlation between growth increases of the cranial base, the maxilla, the ramus, and the effective length of the mandible and growth prediction assessed with the help of hand–wrist radiographs (Verma, Peltomaki, and Jager 2009). However, in a systematic review of literature it was concluded that skeletal maturity assessment using hand-wrist radiographs is correlated to overall skeletal growth velocity and overall facial growth velocity was well related to standing height growth velocity and skeletal maturity. Data from the articles included in the systematic review does not allow meaningful conclusions regarding the relationship of cranial base growth velocity and skeletal maturity (Flores-Mir, Nebbe, and Major 2004).

Through assessing images of the hand-wrist, the age of average pubertal onset in females has been determined to be 10.0 years and ends at 14.8 years. Whereas in males, pubertal onset is on average at age 12.1 and ends at 17.1 years. In both sexes, peak height velocity occurred two years after pubertal onset (Hagg and Taranger 1982).

There are some limitations to the hand-wrist radiographic technique. Polymorphism and sexual dimorphism are common, which can limit clinical prediction (Flores-Mir, Nebbe, and Major 2004). Polymorphism refers to the fact that the hand-wrist bones come in different shapes and forms and therefore may not follow the same developmental pattern. Sexual dimorphism is that there is a difference in the size and appearance between males and females, making characterization of staging more difficult. Furthermore, using hand-wrist radiographs to assess skeletal maturation does require an additional radiograph beyond what is typically used for orthodontic diagnosis and treatment planning. It also requires a lateral cephalometric machine to take a hand-wrist radiograph, which many are moving away from with the increased number of offices using CBCTs.

Cervical Vertebrae Maturation

Cervical vertebrae maturation (CVM) as seen on a lateral cephalogram has also been used as a marker of skeletal maturity since it was first examined in a thesis by Lamparski (Lamparski 1972). Hassel and Farman developed the original CVM index, which has since been modified several times (Hassel and Farman 1995). Use of the CVM analysis eliminates the need for taking an additional radiograph, since orthodontists routinely take lateral cephalograms to properly diagnose and treatment plan their patient's cases. The maturation of the cervical vertebrae is thought to correlate closely with facial growth and therefore a worthwhile skeletal maturation indicator to evaluate (Baccetti, Franchi, and McNamara 2002).

CVM analysis system evaluates the shape of the first four or five cervical vertebrae as seen on a two-dimensional lateral cephalogram. The inferior border of the vertebral body is one of the primary radiographic marker in the CVM analysis system. As a person ages, this inferior border will transition from flat to concave. The second objective is to evaluate the shape of the vertebral bodies. The bodies start out as trapezoidal, then become square and lastly change to a rectangular vertical shape (McNamara and Franchi 2018). Most analyses include five or six cervical vertebrae maturation stages (CVMS). Using the six stage classification system, the greatest increment of mandibular body growth occurs between the stages CVMS 3 and 4, when a concavity develops in the inferior border of the fourth vertebra, and the bodies of all cervical vertebrae become rectangular in both boys and girls. Typically, CVMS 1 and CVMS 2 are considered prepubertal, CVMS 3 and CVMS 4 are circumpubertal, and CVMS 5 and CVMS 6 are postpubertal (McNamara and Franchi 2018) .

Studies examining CVM have disagreed on the reproducibility and reliability of using this maturation indicator to predict growth. One reason that the reliability of CVM is low is the difficulty classifying the shapes of the C3 and C4 vertebrae as square, rectangular, or trapezoidal (Nestman et al. 2011). Several previous studies have decided that inter and intra-observer agreement was only fair to moderate (Gabriel et al. 2009; Sohrabi et al. 2016; Predko-Engel et al. 2015). Gabriel et al. reported an inter-observer reliability at 50% and intra-observer reliability at 62% (Gabriel et al. 2009). The study by Predko-Engel and team similarly reported a low inter-observer reliability of 0.28 and intra-observer reliability of 0.44 (Predko-Engel et al. 2015).These studies conclude that CVM cannot be recommended as a strict clinical guideline for determining orthodontic treatment. The study by Sohrabi et al. reported slightly better inter-observer reliability of 0.48 and intra-observer reliability of 0.72 to 0.74 (Sohrabi et al. 2016).

On the contrary, Franchi et al. concluded that it is straightforward to distinguish the different shapes of the cervical vertebrae and there is high reliability and reproducibility (Franchi, Baccetti, and McNamara 2004). Their inter-observer agreement was 98.6% by trained examiners and intra-observer agreement was 100%. Yet another study by Rainey also determined that CVM was reproducible and reliable. Their intra-observer kappa coefficient was 0.82 with a 95% agreement, when using a standardized sample and the inter-observer kappa coefficient was 0.83 with 92-93% agreement.

It is clear that there is some controversy and disagreement surrounding the use of cervical vertebrae maturation as a skeletal marker for growth. In a systematic review of cervical vertebral maturation as a biological indicator of skeletal maturity, it was concluded that many CVM studies have methodological failures, such as difference in quantitative measurements, not reporting randomization, blinding and sample size calculation. Their conclusion was that better designed studies are needed to determine its accuracy and reliability (Santiago et al. 2012).

Spheno-Occipital Synchondrosis

In the posterior cranial base, the cartilaginous junction between the sphenoid and occipital bones is the area known as the spheno-occipital synchondrosis. This synchondrosis is a primary cartilage that has inherent growth potential. There is an area of cellular hyperplasia in the center with bands of maturing cartilage cells extending in both directions, which will eventually be replaced by bone (Proffit, Fields, and Sarver 2013). The spheno-occipital synchondrosis fusion is thought to correlate closely with growth of the maxillary complex (Saito 1989). The translation of the anterior cranial base and the maxillary complex is due to the growth of the spheno-occipital synchondroses (Coben 1998).

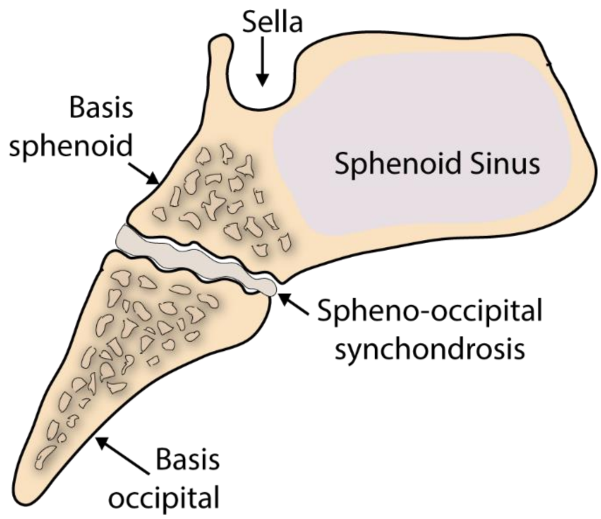


Figure 2: Schematic of the synchondroses of the cranial base

Irwin was one of the first to study the closure of the spheno-occipital synchondrosis, and some early generalizations came from his work (Irwin 1960). He studied histological sections and he noticed that although some narrowing may occur prior to age 9, the synchondrosis generally remains open at that age. It starts to close in some people as early as 11, and the average age that closure starts is age 13. Narrow openings in the inferior aspect of the synchondrosis are seen until age 18, but after that, complete closure is seen.

The research of the spheno-occipital synchondrosis was further expanded upon by examining dry skulls. It determined that closure of the spheno-occipital synchondrosis for females was completed at age 14 and for males at age 15 (Powell and Brodie 1963). Melsen further examined closure of the spheno-occipital synchondrosis during the autopsy of 100 individuals who died from accidents, violence or brief illness (Melsen 1972). She found that ossification of the synchondral cartilage was found to occur in boys at an age of 13-18 years and in girls at an age of 12 -16 years. She determined that the closure started at the clivus, proceeding in a wedge shape from there. Similarly, to the hand-wrist maturation and cervical vertebrae maturation, the spheno-occipital synchondrosis closes about 2 years earlier in females than males (Ingervall and Thilander 1972).

Using high resolution CT scans on a Japanese population of of 253 patients ages 1-77 years a study concluded that the spheno-occipital synchondrosis is closed by age 13 (Okamoto et al. 1996). A cadaver study using CT to visualize the spheno-occipital synchondrosis of an Australian population determined the time of closure was closer to 17 years of age, for both males and females (Bassed, Briggs, and Drummer 2010). However, the population studied in that study was older than previous studies at 15-25 years. It is clear that there is great variability in the closure of the synchondrosis and this is likely due to the populations studied and method of evaluation – radiographic, histological or dry skulls. One caveat to using CBCTs to analyze the synchondrosis is that a tiny ossification center cannot be seen on a radiograph of the skull base. While, on the other hand, a larger ossification center within the synchondrosis may be mistaken for a partially (usually superiorly) or totally closed synchondrosis.

In recent years, several classifications to describe the closure of the spheno-occipital synchondrosis have been developed. Bassed (Bassed, Briggs, and Drummer 2010) modified a five stage system that was originally developed by Powell and Brodie (Powell and Brodie 1963). Kinder further modified this classification system, which is what was used to analyze the spheno-occipital synchondrosis in this study (Kinder 2009). Since the advent of CBCT use by orthodontists, more clinicians have been observing the spheno-occipital synchondrosis closure since it can be clearly seen with this advanced technology. It is important for clinicians to have experience analyzing the different methods of determining skeletal maturation and know their limitations, so they can make an educated assessment of a patient's growth potential.

Previous studies on correlation between maturation indicators

Based on previous studies, it has been proven that there is a statistically significant correlation between hand-wrist maturation and cervical vertebrae maturation. Uysal et al. found the Spearman rank-order correlation coefficient between hand-wrist and cervical vertebrae maturation to be 0.86 (Uysal et al. 2006). This article used a rigorous selection and reporting criteria (Santiago et al. 2012). Pichai et al. also examined the correlation between hand-wrist and cervical vertebrae maturation and found the kappa correlation coefficient to be 0.793, which is similar to another study by Gandini et al., in which the kappa correlation coefficient was 0.783 (Pichai et al. 2014; Gandini, Mancini, and Andreani 2006).

On the other hand, Hoseini et. al. showed a low level of agreement between the stages of CVM and hand-wrist (Hoseini et al. 2016). The highest level of agreement was with the youngest patients in their sample size (ages 8-9) and lowest agreement was with the age group of 12-14 years old. However, each study did use a slightly different analysis to examine the hand-wrist radiographs and cervical vertebrae maturation stages, which could account for the variable levels of agreement.

In the first published study that has compared cervical vertebrae maturation to the spheno-occipital synchondrosis, Fernandez-Perez et al. focused on the comparison as seen on a CBCT (Fernandez-Perez et al. 2016). This study found a strong correlation between the two maturation indicators with the Pearson correlation coefficient of 0.89. They also concluded the spheno-occipital synchondrosis was a good indicator of growth maturation.

In a study of Turkish population, that assessed the correlation between third molar mineralization, spheno-occipital synchondrosis fusion, chronological age and cervical vertebrae maturation for skeletal maturation. The agreement between CVM and spheno-occipital synchondrosis was very strong in men (r=0.851) and strong in females (r=0.618) (Demirturk Kocasarac et al. 2017).

The only published study that shows the agreement between hand-wrist maturation and spheno-occipital synchondrosis closure was a thesis conducted at the University of Tennessee (Hight 1980). However, this study focused on the adductor sesamoid, rather than the third phalanx, which our study focuses on. Furthermore, they used a midsagittal cephalometric laminagraph, whereas ours used CBCT images. This study concluded that the hand-wrist bones and spheno-occipital synchondrosis were moderately correlated to each other.

Cone Beam Computed Tomography

Cone Beam Computed Tomography (CBCT) was introduced to the dental field in 2001 (Hatcher 2010). CBCTs allows the clinician to view a 3-dimensional image of the head and neck region. The x-ray beam moves 360 degrees around the head to capture multiple images of the patient. With a CBCT scan, it is possible to see high quality images of bone, teeth, sinuses, and the temporomandibular joint. From the CBCT, panoramic, frontal cephalometric and lateral cephalometric, among other images can be extracted using imaging software, such as Dolphin Imaging, which was used in this study. The CBCT and the extracted images are used for orthodontic diagnosis and treatment planning. It can also be helpful for determining positions of impacted teeth, surgical treatment planning and placement of mini-implants or TADs.

Although one CBCT scan may replace all conventional orthodontic radiographs one set of conventional radiographs is still 2-4 times less radiation than one CBCT. Depending on the scan mode, the radiation dose of a CBCT is about 3-6 times a panoramic radiograph and 15-26 times a lateral cephalogram. (Signorelli et al. 2016) . Therefore, when using a CBCT routinely on every patient, it should be thoroughly utilized. This includes examining the amount of closure of the spheno-occipital synchondrosis.

The radiation dose from CBCT machines depends on the unit type, field of view, image resolution and other factors (Ludlow et al. 2015; Grunheid et al. 2012).

Specific Aims

- This study seeks to assess the degree of agreement between hand-wrist, cervical vertebrae and spheno-occipital synchondrosis maturation stages for skeletal age determination.
- This study will compare all three maturation indicators to each other and to age for both the male and female genders.
- This research will allow an orthodontist to compare these common skeletal maturation indices: Baccetti's analysis of CVM (Baccetti, Franchi, and McNamara 2002), Hagg and Taranger's analysis of hand-wrist radiographs (Hagg and Taranger 1982), and Kinder's Classification of the spheno-occipital synchondrosis (Kinder 2009).
- The study also analyzed both intra and inter-examiner reliability of the different analyses to determine which is the most reliable.

Hypothesis

- We hypothesize that the analysis of markers traditionally used for determination of skeletal maturity (hand-wrist maturation, cervical vertebrae maturation, and spheno-occipital synchondrosis closure) will correlate to each other and chronological age, regardless of gender.
- Knowledge of how the maturation indicators relate in terms of pre-peak growth, peak growth and post-peak growth will help orthodontists to determine how much growth is remaining and consequently, when to best treat a patient.
- We also hypothesize that each of the three skeletal maturation indicators will positively correlate to age.
- Lastly, we hypothesized that the stages for the female subjects will mature earlier than for the male subjects

Materials & Methods

Research Design

This study retrospectively compared the hand-wrist maturation, cervical vertebrae maturation, and spheno-occipital synchondrosis closure of 61 patients. The subjects for this study were all patients at the University of Minnesota Orthodontic Clinic and the radiographs were obtained as part of the diagnostic records for their orthodontic treatment. The population consisted of 33 females and 28 males ages 9.5 to 17.5. The age distribution of subjects can be seen in Table 1. The radiographs were obtained from the years 2012-2017 in the University of Minnesota's School of Dentistry Radiology Department. All radiographs were acquired by a licensed dental radiology technician.

Age Group	Number of subjects (N)
9.5-11	2
11.5-12.5	22
13-14	23
14.5-15.5	9
16-17.5	5

Table 1: Age distribution of subjects

All subjects included in this study signed a consent form that allowed their records to be used for research purposes. The Institutional Review Board (IRB) of to the University of Minnesota exempted this study from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS.

To be included in the study, subjects must have had CBCT with extended field of view and hand-wrist radiograph taken within three months of each other. The subjects we used were chosen because they had hand-wrist radiographs, which was the limiting factor, since not every patient in our clinic had one. The patient's all had hand-wrist radiographs because they were the patients of one certain faculty, who required hand-wrist radiographs on all of his adolescent patients. The age at the time of the radiograph was recorded to the nearest half year. Gender was also recorded, but the readers that interpreted the radiographs were blinded to any information about the subjects of the radiographs. Race was not recorded. There were no age, gender, or race restrictions. Patients were excluded from the study if they had a craniofacial syndrome, head/neck/hand trauma/deformity or the radiographs were not of diagnostic quality, as determined by the radiologist.

To reduce variability, the same machines were used to take radiographs and software was used to interpret the radiographs. For our study, all the CBCT scans were acquired with Next Generation iCAT CBCT unit (Imaging Sciences International, Hatfield, PA). The hand-wrist radiographs were obtained with Orthopantomograph OP200 and OP200D (Instrumentarium Dental, Tuusula, Finland).

There were three examiners that read and analyzed the radiographs: an oral-maxillofacial radiologist, an orthodontic resident and a dental student. All examiners were calibrated in the same training session to use the three methods of analysis indicated. During the calibration session, the oral and maxillofacial radiologist reviewed and explained each analysis thoroughly. For each skeletal maturation indicator, ten random radiographs were interpreted, and the readers collectively discussed which stage would be most appropriate for that image. After each reader felt comfortable with the analyses, the reading portion of the study commenced. During the analysis, each examiner read the radiographs at two separate time points two weeks apart and in a random order. Each reader was positioned so that they could not see the other reader's staging responses, but they were in the same room and saw the same images on the same screen for the same amount of time.

The independent variables are the three different maturation indices and the ages of the patients, while the dependent variable is the stage of growth that the patient is at. In this study, one of the confounding variables is the number of hand-wrist radiographs obtained in our clinic, since not all faculty members require them, there is a limited number for use. Another confounding variable is the bias of observers. In this study, the observers have three different levels of education and experiences using the maturation indicators prior to the study. Therefore, despite calibration, biases may impact how radiographs are interpreted.

Cervical Vertebrae Image

Dolphin imaging software (Dolphin Imaging & Marketing Solutions, Chatsworth, CA) was used to extract the CVM images from the CBCT. It has been shown that the CVM visualized on CBCTs is just as accurate as if viewed on a lateral cephalogram (Joshi et al. 2012). In order to eliminate any confounding variables, all were extracted in the same manner. Each CBCT volume was oriented with both orbitales parallel to the floor from a coronal view and with porion and orbitale parallel to the floor from a sagittal view. Then from the sagittal view of the mid-sagittal plane, the cervical vertebrae were isolated so that no teeth or other markers, such as the spheno-occipital synchondrosis, could be seen (Figure 3). This image was saved, de-identified and given a random number 1-61.

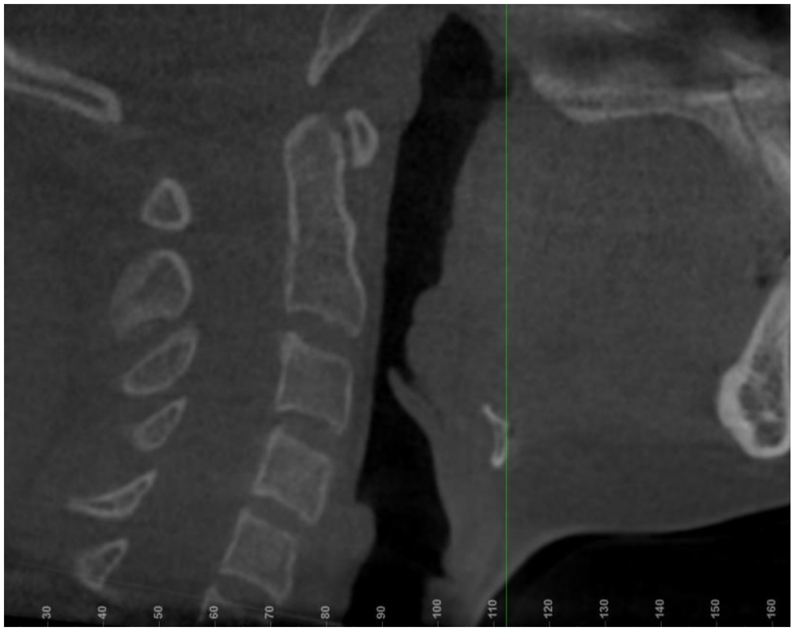


Figure 3: Example of CVM image

Hand-wrist radiograph

The hand-wrist radiographs were taken with Orthopantomograph OP200 and OP200D. . They were not manipulated in any way and were used exactly how they were uploaded into dolphin imaging software. All were de-identified and assigned a random number 1-61. This number was the same number given to the CVM and spheno-occipital synchondrosis images.

Figure 4: Example of hand-wrist radiograph

Spheno-occipital synchondrosis:

In order to interpret the spheno-occipital synchondrosis the iCAT imaging software was used. All of the CBCT's were de-identified using OnDemand3D software (CyberMed, Seoul, South Korea). A small field of view the speheno-occipital synchondrosis was used to eliminate confounding factors such as teeth or the cervical vertebrae. While analyzing, the spheno-occipital synchondrosis was scrolled through in a sagittal manner to allow the observer to see any closure that may be present, since not all ossification occurs at the midline. Figure 5 displays an example of a sagittal slice of the spheno-occipital synchondrosis as seen on a CBCT

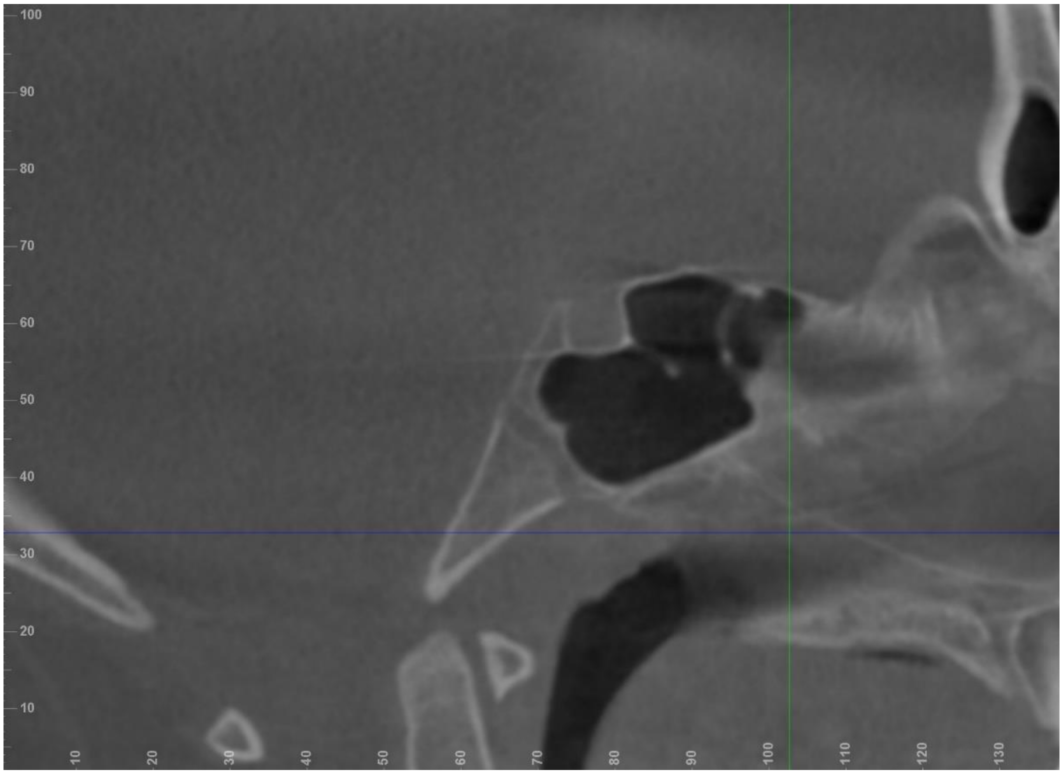


Figure 5: Example of Spheno-occipital synchondrosis radiograph

Study Methods

The three methods of analysis used in this research study are Baccetti's CVM analysis (Baccetti, Franchi, and McNamara 2005), Hagg and Taranger's Hand-Wrist analysis (Hagg and Taranger 1982), and Kinder's spheno-occipital synchondrosis analysis (Kinder 2009) . These three methods were chosen because of their ease of use and since they all have five stages; the analyses were more straightforward as well.

Baccetti's CVM analysis

Baccetti's analysis examines the morphological changes of the cervical vertebrae and breaks down the maturation into five stages (Baccetti, Franchi, and McNamara 2002). As growth progresses, the inferior portion of the vertebrae curve and elongate. The stages are:

- CVMS I (Stage 1): The lower borders of C2-C4 are flat, bodies of C3 and C4 are trapezoidal, and peak mandibular growth is two years after.
- CVMS II (Stage 2): There is a concavity on lower border C2. C3 and C4 still trapezoidal and peak mandibular growth is one year after this stage.
- CVMS III (Stage 3): There are concavities at the lower border of both C2 and C3, bodies of C3 and C4 are either trapezoidal or rectangular and peak mandibular growth occurs during the year after this stage.
- CVMS IV (Stage 4): Concavities exist at the lower border of C2, C3, C4 are now present, bodies of C3 and C4 are rectangular, and peak mandibular growth has occurred within one or two years before this stage.
- CVMS V (Stage 5): The concavities of C2, C3, C4 are still present. C3 and C4 are either rectangular or squared in shape, and peak mandibular growth has ended at least one year before.

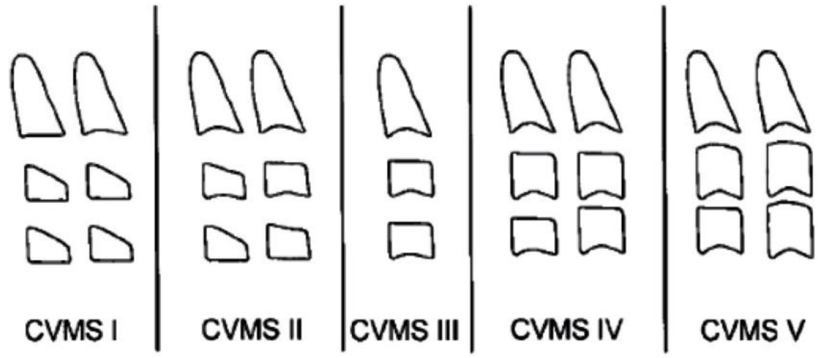


Figure 6: Schematic representation of Baccetti's CVM analysis

According to McNamara, in the five-stage version of the CVM analysis, stage III most closely correlates to peak growth. For this study, stages I and II were grouped into pre-pubertal, stage III was considered peak-growth and stages IV and V were post-peak growth (McNamara and Franchi 2018).

Hagg and Taranger Hand-Wrist Analysis

To analyze the hand-wrist radiographs, Hagg and Taranger's analysis was used (Hagg and Taranger 1982). This analysis, which is a modified version of Fishman's analysis (Fishman 1982), has five stages and focuses on the middle phalanx of the middle finger.

- MP3F stage (Stage 1): Epiphysis is as wide as metaphysis and it denotes the onset of pubertal growth spurt.
- MP3FG stage (Stage 2): Epiphysis is as wide as metaphysis and there is a distinct lateral border of the epiphysis forming a line of demarcation at right angle to the lateral border.

- MP3G stage (Stage 3): The sides of the epiphysis have thickened and also capped its metaphysis forming a sharp edge distally at one or both. This stage indicates peak growth spurt.
- MP3H stage (Stage 4): Fusion of epiphysis and metaphysis has begun. It is the deceleration period of pubertal growth spurt.
- MP3I stage (Stage 5): Fusion of epiphysis and metaphysis was complete. It marks the end of pubertal growth spurt.

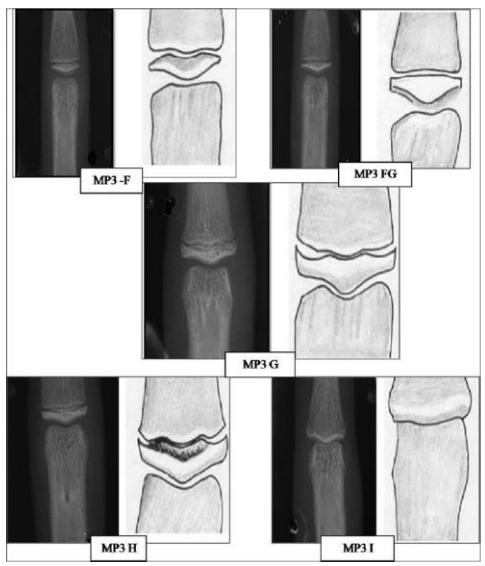


Figure 7: Schematic representation of Hagg and Taranger's hand-wrist analysis

For this analysis, MP3F and MP3FG (stages 1 & 2) were considered pre-peak growth, MP3G (stages 3) was considered peak growth and MP3H and MP3I (stages 4 & 5) were considered post-growth (Madhu, Hegde, and Munshi 2003).

Kinder’s Spheno-Occipital Synchondrosis Analysis

To analyze the spheno-occipital synchondrosis Kinder’s classification was employed. This classification examines the amount of fusion of the spheno-occipital synchondrosis as seen while moving through sagittal slices of a CBCT. The stages of Kinder’s Analysis are:

- Grade 1 (Stage 1): The synchondrosis is patent, without any center of ossification.
- Grade 2 (Stage 2): The synchondrosis is patent, and one center of ossification is present.
- Grade 2 (Stage 3): The synchondrosis is patent, and more than one centers of ossification are present.
- Grade 4 (Stage 4): The synchondrosis is incompletely fused, the outlines of the synchondrosis are detectable
- Grade 5 (Stage 5): The synchondrosis is completely fused and the outline is not detectable.

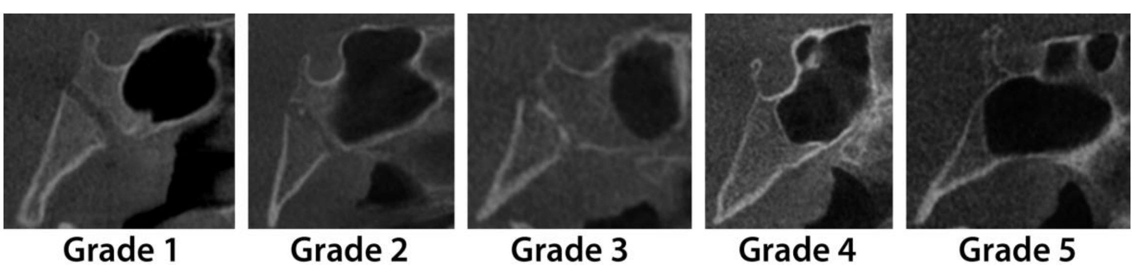


Figure 8: Kinder’s classification of spheno-occipital synchondrosis

Fernandez et al. determined that peak pubertal growth corresponded to grade 3 (Fernandez-Perez et al. 2016). Therefore, for the purposes of the analysis, Grade 1 and 2 were grouped together as pre-peak growth, Grade 3 was considered peak growth and Grade 4 and 5 were considered post-peak growth.

Results

Inter-rater and intra-rater agreement

The intra-rater agreement is the degree of agreement among repeated administrations of grading the skeletal maturation indicators as performed by a single rater. This was assessed using both weighted kappa statistics and Kendall's coefficient of concordance. This was calculated by comparing the first and second dates of data collection of each analysis for each reader individually, then the average was taken. The inter-rater agreement was assessed for both dates of reading to determine the agreement between all three readers. The average of both dates was calculated. Inter-rater agreement was only analyzed using Kendall's coefficient of concordance because this statistic is more appropriate when there are more than two readers. For interpretation of Kappa: < =0 is poor; 0-0.2 is slight; 0.2-0.4 is fair; 0.4-0.6 is moderate; 0.6-0.8 is substantial and 0.8-1 is almost perfect (Viera and Garrett 2005). For Kendall's coefficient, 0 means there is no agreement, and 1 is unanimous agreement.

The average intra-rater agreement calculated by weighted kappa for cervical vertebrae maturation was 0.771, and 0.936 as calculated by Kendall's coefficient, both of which are considered substantial agreement (Table 2). For hand wrist maturation, the average intra-rater agreement was 0.895 (weighted Kappa) and 0.979 (Kendall's coefficient) which is considered near perfect agreement (Table 3). The average intra-rater agreement for the spheno-occipital synchondrosis closure was 0.642

calculated by weighted kappa and 0.8981 calculated by Kendall's coefficient, which is substantial agreement (Table 4).

Reader (Parameter)	1-5 scale weighted Kappa	1-5 scale Kendall's coefficient
Reader #1 (CVM)	0.7831	0.9555
Reader #2 (CVM)	0.7553	0.9320
Reader #3 (CVM)	0.7744	0.9211
Average	0.771	0.936

Table 2: Intra-rater agreement for CVM

Reader (Parameter)	1-5 scale weighted Kappa	1-5 scale Kendall's coefficient
Reader #1 (HW)	0.9152	0.9808
Reader #2 (HW)	0.8764	0.9747
Reader #3 (HW)	0.8924	0.9822
Average	0.895	0.979

Table 3: Intra-rater agreement for Hand-Wrist (HW)

Reader (Parameter)	1-5 scale weighted Kappa	1-5 scale Kendall's coefficient
Reader #1 (SOS)	0.7372	0.9457
Reader #2 (SOS)	0.6759	0.8850
Reader #3 (SOS)	0.5128	0.8626
Average	0.642	0.8981

Table 4: Intra-rater agreement for Spheno-Occipital Synchondrosis (SOS)

This study showed that the average inter-rater agreement for CVM is 0.892 (Kendall's coefficient) (Table 5). Average inter-rater agreement for hand-wrist is 0.972 (Kendall's coefficient) (Table 6). Average inter-rater agreement for spheno-occipital synchondrosis is 0.886 (Kendall's coefficient) (Table 7). All of these are indicative of moderately high agreement.

CVM	1-5 scale Kendall's Coefficient
Date #1	0.8972
Date #2	0.8869
Average	0.892

Table 5: Inter-rater agreement for CVM

Hand-Wrist	1-5 scale Kendall's Coefficient
Date #1	0.9673
Date #2	0.9762
Average	0.972

Table 6: Inter-rater agreement for HW

Spheno-occipital Synchondrosis	1-5 scale Kendall's Coefficient
Date #1	0.8893
Date #2	0.8827
Average	0.886

Table 7: Inter-rater agreement for spheno-occipital synchondrosis

Agreement between skeletal maturation indicators

The agreement of the three maturation indicators was assessed to discern how well they relate to each other. Two parameters were compared at a time. This was done for each individual reader based from the data collected the first date of reading and then based on a consensus that was made. The consensus of what stage the individual was at for each parameter was determined using the following rules: if all three reader's stages agree, that stage was used; if two of the reader's agreed and the third disagreed, then the stage of the two that agreed was used; if none of the reader's stages agreed, then an average of all three stages rounded to the nearest whole number was used. This consensus is utilized throughout the analysis. The consensus agreement between the maturation indicators was determined for the numerical 1-5 scale as well as the three statuses (pre-peak, peak and post-peak growth).

The weighted kappa statistic was determined for each of the readers individually and then based on a consensus. The p-value was also calculated to show significance. The agreement between hand-wrist to cervical vertebrae, cervical vertebrae to spheno-occipital synchondrosis and hand-wrist to spheno-occipital can be seen in tables 8 and 9 below.

Rater	**CVM vs. HW**	**CVM vs. SOS**	**HW vs. SOS**
Rater #1	0.5063 (<.0001)	0.3467 (<.0001)	0.5520 (<.0001)
Rater #2	0.3829 (<.0001)	0.0947 (0.1678)	0.3920 (<.0001)
Rater #3	0.4474 (<.0001)	0.2595 (0.0005)	0.4550(<.0001)
Consensus	0.4563 (<.0001)	0.2511 (0.0008)	0.5079 (<.0001)

Table 8: Weighted Kappa statistics is calculated to show the agreement between two different parameters for the scale of 1-5. P-value is in the parenthesis.

Rater	**CVM vs. HW**	**CVM vs. SOS**	**HW vs. SOS**
Rater #1	0.6205 (<0.0001)	0.4792 (<0.0001)	0.6092 (<0.0001)
Rater #2	0.4945 (<0.0001)	0.1804 (0.0495)	0.4397 (<0.0001)
Rater #3	0.4722 (<0.0001)	0.3009 (0.0015)	0.5156 (<0.0001)
Consensus	0.5421 (<0.0001)	0.3177 (0.0011)	0.5492 (<0.0001)

Table 9: Weighted Kappa statistics is calculated to show the agreement between two different parameters for the scale of pre, peak and post-peak pubertal growth. P-value is in the parenthesis.

Spearman Correlation Coefficients, N = 61 Prob > |r| under H0: Rho=0			
	CVM_CONSENSUS	**HW_CONSENSUS**	**SOS_CONSENSUS**
CVM_CONSENSUS CVM_Consensus	1.00000	0.68456 <.0001	0.51969 <.0001
HW_CONSENSUS HW_Consensus	0.68456 <.0001	1.00000	0.73655 <.0001
SOS_CONSENSUS SOS_Consensus	0.51969 <.0001	0.73655 <.0001	1.00000

Table 10: Spearman Correlation Coefficient for the consensus between each two of the maturation indicators. P-value is also calculated.

In table 11, the comparison of the three maturation indicators was broken down by gender, to determine if there was a closer correlation with either the female or male population. These should not be overinterpreted, because by chance there will always be some difference.

Variables	Gender	5-scale
CVM vs. HW	F	0.443 (<.0001)
	M	0.482 (0.0002)
CVM vs. SOS	F	0.208 (.0006)
	M	0.334 (0.007)
HW vs. SOS	F	0.497 (<.0001)
	M	0.484 (<0.0001)

Table 11: Comparison of each pair of the skeletal maturation indicators broken down by gender. P-value is in parenthesis.

The table 12 and figure 9 below display the frequencies of stages of cervical vertebrae and hand -wrist as well as the cross-tabulation of vertebrae by hand-wrist maturation. Individual scores of cervical vertebrae and hand-wrist maturational stages are given.

HW	CVM					Total
	1	2	3	4	5	
1	4	3		1		8
2	9	2	1	1		13
3	1	3	3	4		11
4	1	1	4	4	1	11
5		1	4	6	7	18
Total	15	10	12	16	8	61

Table 12: Frequency of CVM vs. HW

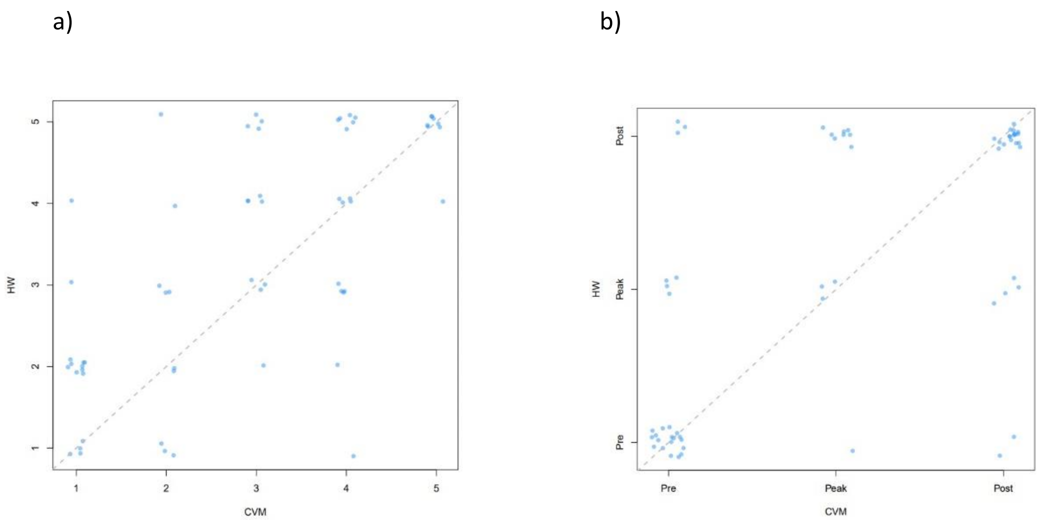


Figure 9: a) graph indicating correlation between HW and CVM using 1-5 scale. b) graph indicating correlation between HW and CVM using pre, peak and post-peak pubertal growth scale.

The table 13 and figure 10 below display the frequencies of stages of cervical vertebrae stages and spheno-occipital synchondrosis stages as well as the cross-tabulation of vertebrae by spheno-occipital synchondrosis maturation. Individual scores of cervical vertebrae and spheno-occipital maturational stages are given.

SOS	CVM					Total
	1	2	3	4	5	
1	2		1			3
2	5	3		1		9
3	5	3	1	4	1	14
4	3	3	5	6	4	21
5		1	5	5	3	14
Total	15	10	12	16	8	61

Table 13: Frequency of CVM vs. SOS

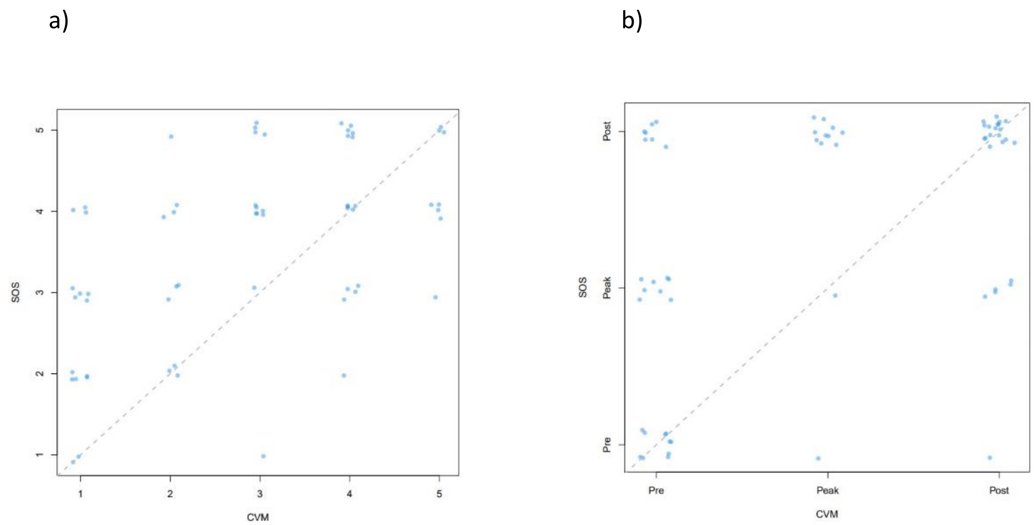


Figure 10: a) graph indicating correlation between SOS and CVM using 1-5 scale. b) graph indicating correlation between SOS and CVM using pre, peak and post-peak pubertal growth scale.

The table 14 and figure 11 below display the frequencies of stages of spheno-occipital synchondrosis and hand-wrist maturation as well as the cross-tabulation of spheno-occipital synchondrosis by hand-wrist maturation. Individual scores of spheno-occipital synchondrosis and hand-wrist maturational stages are given.

HW	SOS					Total
	1	**2**	**3**	**4**	**5**	
1	1	4	2	1		8
2		5	6	2		13
3	1		4	6		11
4	1		1	6	3	11
5			1	6	11	18
Total	3	9	14	21	14	61

Table 14: Frequency of HW vs. SOS

a) b)

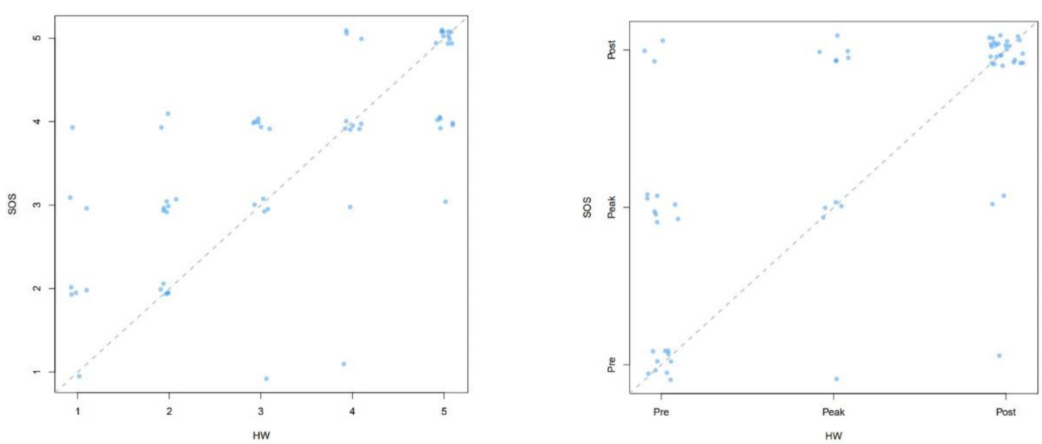


Figure 11: a) graph indicating correlation between HW and SOS using 1-5 scale. b) graph indicating correlation between HW and SOS using pre, peak and post-peak pubertal growth scale.

Correlation to Age

For each stage of skeletal maturation indicator, the mean age, median age, minimum and maximum age and interquartile range was determined. The p-value and the Pearson correlation coefficient were calculated. This was also calculated for the three statuses – pre-peak growth, peak growth and post-peak growth.

Maturation Indicator	Category	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	P-value
CVM consensus	n	15	10	12	16	8	<0.0001
	Median	12.00	12.50	13.50	13.50	15.00	
	Mean (SD)	12.23 (1.10)	12.45 (0.44)	13.33 (1.25)	13.75 (1.35)	15.13 (1.48)	
	(Min, Max)	(9.50, 13.50)	(12.00, 13.00)	(11.50, 15.00)	(12.00, 16.50)	(13.50, 17.50)	
	IQR	(11.50, 13.00)	(12.00, 13.00)	(12.00, 14.25)	(12.75, 14.50)	(13.75, 16.25)	
HW consensus	n	8	13	11	11	18	<0.0001
	Median	12.00	12.50	12.50	13.50	14.25	
	Mean (SD)	12.06 (1.18)	12.38 (0.79)	12.95 (1.49)	13.59 (0.89)	14.42 (1.49)	
	(Min, Max)	(9.50, 13.50)	(11.00, 13.50)	(11.50, 16.50)	(12.00, 15.00)	(12.00, 17.50)	
	IQR	(12.00, 12.75)	(12.00, 13.00)	(12.00, 13.00)	(13.00, 14.50)	(13.50, 15.50)	
SOS consensus	n	3	9	14	21	14	0.0146
	Median	13.00	12.00	12.25	13.00	14.00	
	Mean (SD)	12.67 (1.04)	12.33 (0.79)	12.71 (1.77)	13.50 (1.31)	14.18 (1.37)	
	(Min, Max)	(11.50, 13.50)	(11.00, 13.50)	(9.50, 16.50)	(12.00, 16.50)	(12.00, 17.50)	
	IQR	(11.50, 13.50)	(12.00, 12.50)	(12.00, 13.00)	(12.50, 14.50)	(13.00, 14.50)	

Table 15: Age relations to each maturation indicator based on the 1-5 scale

Maturation indicator	Category	Pre	Peak	Post	P-value
CVM status consensus	n	25	12	24	<0.0001
	Median	12.50	13.50	14.00	
	Mean (SD)	12.32 (0.89)	13.33 (1.25)	14.21 (1.52)	
	(Min, Max)	(9.50, 13.50)	(11.50, 15.00)	(12.00, 17.50)	
	IQR	(12.00, 13.00)	(12.00, 14.25)	(13.00, 15.25)	
HW status consensus	n	21	11	29	<0.0001
	Median	12.00	12.50	14.00	
	Mean (SD)	12.26 (0.94)	12.95 (1.49)	14.10 (1.34)	
	(Min, Max)	(9.50, 13.50)	(11.50, 16.50)	(12.00, 17.50)	
	IQR	(12.00, 13.00)	(12.00, 13.00)	(13.00, 14.50)	
SOS status consensus	n	12	14	35	0.0054
	Median	12.25	12.25	13.50	
	Mean (SD)	12.42 (0.82)	12.71 (1.77)	13.77 (1.36)	
	(Min, Max)	(11.00, 13.50)	(9.50, 16.50)	(12.00, 17.50)	
	IQR	(12.00, 13.25)	(12.00, 13.00)	(13.00, 14.50)	

Table 16: Age relations to each maturation indicator based on the pre, peak and post-peak pubertal scale

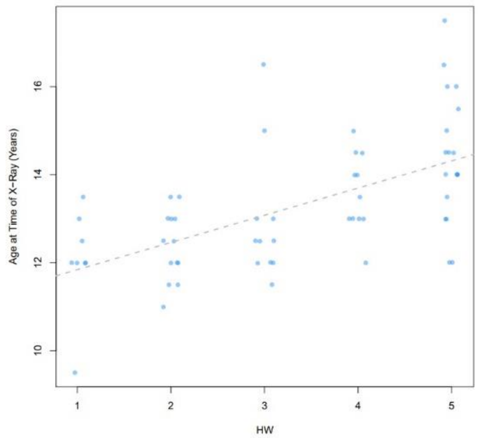
Maturation indicator		Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	p-value
CVM consensus	n	8	6	8	7	4	
	Median	11.75	12.25	13.50	13.00	13.75	
	Mean (SD)	11.56 (1.02)	12.33 (0.41)	13.38 (1.06)	13.29 (0.91)	13.88 (0.48)	<0.001
	(Min, Max)	(9.50, 13.00)	(12.00, 13.00)	(12.00, 15.00)	(12.00, 14.50)	(13.50, 14.50)	
	IQR	(11.38, 12.00)	(12.00, 12.5)	(12.75, 14.00)	(12.75, 14.00)	(13.50, 14.12)	
HW consensus	n	4	6	5	6	12	
	Median	12.00	11.75	12.50	13.25	14.00	
	Mean (SD)	11.38 (1.25)	11.92 (0.74)	12.40 (0.42)	13.25 (0.76)	13.62 (0.96)	<0.001
	(Min, Max)	(9.50, 12.00)	(11.00, 13.00)	(12.00, 13.00)	(12.00, 14.00)	(12.00, 15.00)	
	IQR	(11.38, 12.00)	(11.50, 12.38)	(12.00, 12.50)	(13.00, 13.88)	(13.00, 14.12)	
SOS consensus	n	0	3	6	14	10	
	Median		12.00	11.75	13.00	14.00	
	Mean (SD)		11.67 (0.58)	11.50 (1.05)	12.89 (0.79)	13.75 (0.86)	<0.001
	(Min, Max)		(11.00, 12.00)	(9.50, 12.50)	(12.00, 14.50)	(12.00, 15.00)	
	IQR		(11.50, 12.00)	(11.50, 12.00)	(12.12, 13.38)	(13.25, 14.00)	

Table 17: Age statistics for females

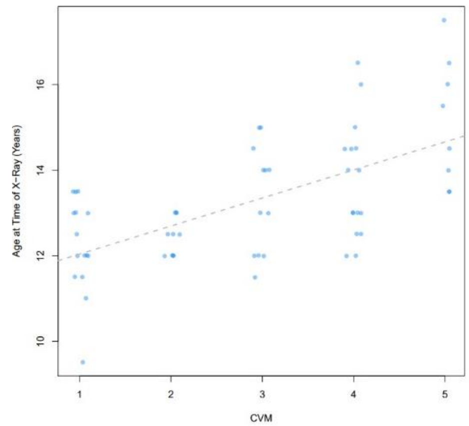
Maturation indicator		Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	p-value
CVM consensus	n	7	4	4	9	4	
	Median	13.00	12.75	13.25	14.50	16.25	
	Mean (SD)	13.00 (0.58)	12.62 (0.48)	13.25 (1.76)	14.11 (1.58)	16.38 (0.85)	0.001
	(Min, Max)	(12.00, 13.50)	(12.00, 13.00)	(11.50, 15.00)	(12.00, 16.50)	(15.50, 17.50)	
	IQR	(12.75, 13.50)	(12.38, 13.00)	(11.88, 14.62)	(13.00, 15.00)	(15.88, 16.75)	
HW consensus	n	4	7	6	5	6	
	Median	12.75	13.00	12.75	14.50	16.00	
	Mean (SD)	12.75 (0.65)	12.79 (0.64)	13.42 (1.93)	14.00 (0.94)	16.00 (1.00)	<0.001
	(Min, Max)	(12.00, 13.50)	(12.00, 13.50)	(11.50, 16.50)	(13.00, 15.00)	(14.50, 17.50)	
	IQR	(12.38, 13.12)	(12.25, 13.25)	(12.12, 14.50)	(13.00, 14.50)	(15.62, 16.38)	
SOS consensus	n	3	6	8	7	4	
	Median	13.00	12.50	13.00	15.00	15.25	
	Mean (SD)	12.67 (1.04)	12.67 (0.68)	13.62 (1.69)	14.71 (1.35)	15.25 (1.94)	0.03
	(Min, Max)	(11.50, 13.50)	(12.00, 13.50)	(12.00, 16.50)	(13.00, 16.50)	(13.00, 17.50)	
	IQR	(12.25, 13.25)	(12.12, 13.25)	(12.38, 14.75)	(13.75, 15.50)	(14.12, 16.38)	

Table 18: Age statistics for males

a)



b)



c)

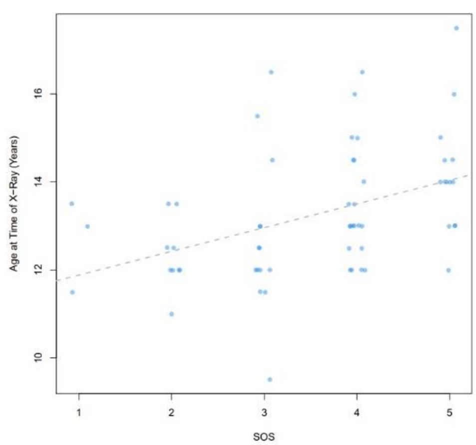
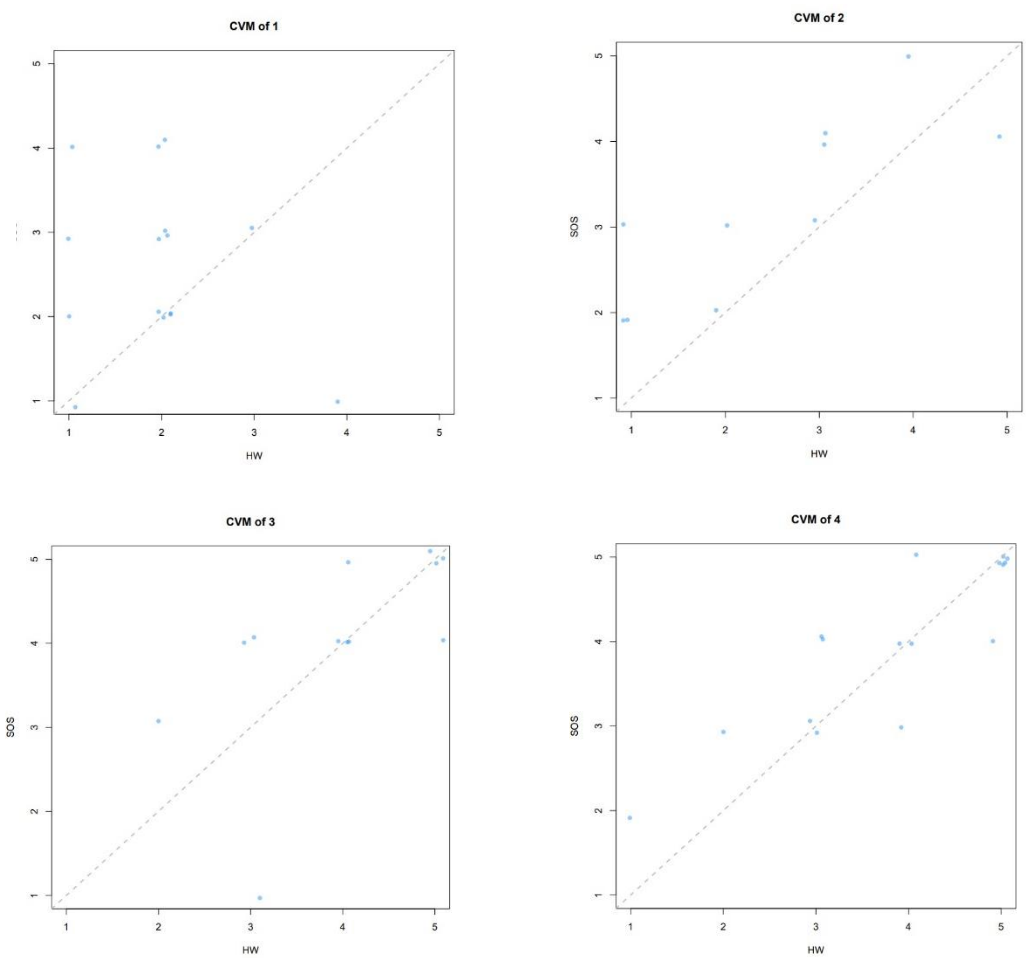


Figure 12: a) Age at time of x-ray in relation to CVM 1-5 scale. b) Age at time of x-ray in relation to HW 1-5 scale. c) Age at time of x-ray in relation to SOS 1-5 scale.

Agreement of all three maturation indicators

Graphs (Figure 13) were used to visualize the correlation between the three maturation indicators. Each cervical vertebra stage was used as the basis and the hand-wrist maturation and spheno-occipital synchondrosis stage were compared to it. There is no statistic that accurately represents the relationship between all three.



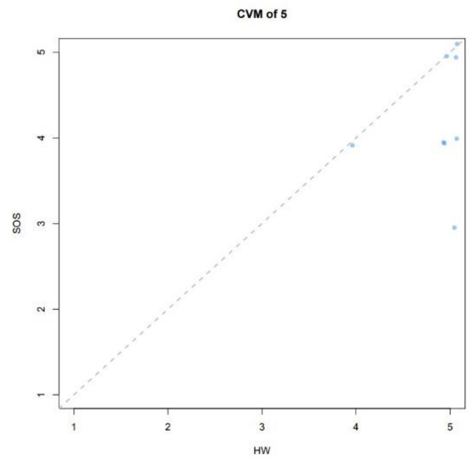


Figure 13: Three-way comparison of the skeletal maturation indicators for each stage using CVM as the base.

Discussion

Summary of Results

We studied the reliability and correlation between three skeletal maturation indicators – hand-wrist maturation, cervical vertebrae maturation and spheno-occipital synchondrosis closure. Our results showed that the hand-wrist maturation analysis had the highest intra and inter-examiner reliability. The hand-wrist maturation and spheno-occipital synchondrosis had the highest level of agreement between the three skeletal maturation indicators. The results also show the relation of age to each stage of the skeletal maturation analyses and that the spheno-occipital synchondrosis closure has the lowest correlation to an increase in age.

Inter-rater and intra-rater agreement

Cervical Vertebrae Maturation

As mentioned in the literature review, the reliability of the cervical vertebrae maturation index has been continuously debated. Many previous studies have assessed the reliability of the cervical vertebrae maturation by examining the inter-rater and intra-rater agreement and there are a wide range of results. Several studies have found there to be significant agreement such as Fernandez-Perez's study (Fernandez-Perez et al. 2016). The inter-rater and intra-rater agreement coefficients for cervical vertebrae maturation were almost perfect; these were $\kappa = 0.90$, and $\kappa = 0.95$ respectively. In yet another study, Rainey found their intra- and inter-observer agreement were substantial at κ = 0.70 and κ = 0.68 respectively (Rainey, Burnside, and Harrison 2016). However, other studies found moderate to lower agreement. In Sohrabi's study, inter-observer agreement was κ = 0.48 and intra-observer agreement values were calculated at κ = 0.59–0.85 for the five observers using the CVMS method, which is considered moderate (Sohrabi et al. 2016). Predko-Engel et. Al. found the reliability to be even lower with κ = 0.44 (intra-rater agreement) and κ = 0.28 (inter-rater agreement) (Predko-Engel et al. 2015).

In our study, the average intra-rater agreement calculated by weighted kappa for cervical vertebrae maturation was 0.771 and average inter-rater was 0.892 (Kendall's coefficient). Our research concluded that there was moderate, but not perfect agreement. Compared to other similar studies, our intra and inter-rater agreement was about average. Some of the variability can be attributed to the CVM assessment method used and number of raters. Our study had three raters, and high agreement between three people is much harder to achieve than agreement between two people. It is important to note that the intra-rater kappa index for each individual was relatively consistent. The experience of the raters is another variable that must be considered. In many of the previous studies, the readers had previous experience with the analysis, which could make them more proficient, but also add an inherent bias. In our study, only the orthodontic resident (reader #1) had used CVM analysis before, and their intra-rater kappa was the highest.

Hand-Wrist Maturation

Interestingly, there are much fewer studies that report upon hand-wrist reliability compared to the abundance of studies that report CVM reliability. In one study that does discuss reliability, the intra-examiner reliability assessed by intraclass correlation coefficient was considered good and ranged from 0.80-0.90 depending on the stage. The inter-examiner evaluation scored excellent (0.92) (Cunha et al. 2018). In our study, the hand-wrist maturation reliability was similar. The average intra-rater agreement was 0.895 (weighted Kappa) and inter-rater agreement was 0.972 (Kendall's coefficient). This indicates a high level of agreement; therefore, it can be considered a reliable indicator. It is also important to note that all three of the raters had a similar intra-rater reliability. This may indicate that experience is not as important of a factor for interpreting this analysis.

Spheno-occipital Synchondrosis Closure

The intra-rater reliability for spheno-occipital synchondrosis closure was 0.642 calculated by weighted kappa, and the average inter-rater agreement for SOS is 0.886 (Kendall's coefficient). In Bassed's research, their intra-examiner agreement of 0.907 (weighted kappa) and inter-examiner agreement of 0.780 (weighted kappa) were considered moderate and substantial respectively (Bassed, Briggs, and Drummer 2010). In Fernandez-Perez's study, the inter and intra-rater agreement coefficients were almost perfect; these were $\kappa = 0.92$, and $\kappa = 0.92$ respectively (Fernandez-Perez et al. 2016). The intra-rater reliability was significantly lower in our study, there are several explanations for this. First, in our study we did utilize the capability of the CBCT software to scan sagittally through the spheno-occipital synchondrosis. This allowed us to visualize more of the synchondrosis than just the midline, which was used in both Bassed's and Fernandez-Perez's studies. The way we viewed the synchondrosis was helpful because ossification may not begin at the midline, but it introduces more room for error. Secondly, the raters in this study had little experience viewing the spheno-occipital synchondrosis, while in the other studies it is stated that experienced observers viewed the images. Of all the maturation indicators tested, the spheno-occipital synchondrosis had the greatest difference between the three reader's intra-examiner kappa index, with a range of three-tenths.

Summary of intra-rater and inter-rater agreement

Overall, in our study, the hand-wrist maturation index had both the highest intra and inter-rater agreement (kappa = 0.895 and Kendall's coefficient = 0.972 respectively). The spheno-occipital synchondrosis had the lowest intra-rater agreement ($\kappa = 0.642$) and average inter-rater agreement 0.886 (Kendall's coefficient). For cervical vertebrae maturation intra-rater agreement was $\kappa = 0.771$ and average inter-rater agreement of 0.892 (Kendall's coefficient). All three have substantial to near perfect agreement. This indicates that the hand-wrist maturation analysis has the highest consistency and the stages of maturation are clearer.

It can be concluded that the hand-wrist analysis is the most reliable between readers because it is easier to discern what stage the epiphysis in the hand-wrist is at because the stages are more distinct compared to the cervical vertebrae maturation and spheno-occipital synchondrosis in which the stages are more fluid. The progression of stages is less well defined for the CVM and spheno-occipital synchondrosis and are subject to interpretation.

For the hand-wrist and cervical vertebrae maturation, the intra-rater agreement was relatively consistent between the three raters. For the spheno-occipital synchondrosis closure, the intra-rater agreements had the most variability; it was the lowest for reader 3 and highest for reader1. Reader 3 was the dental student with the least experience with maturation indicators, and reader 1 was the orthodontic resident, who looks at them more on a day to day basis. The radiologist (reader 2) has the most experience with interpreting radiographs but does not analyze skeletal maturation indicators regularly. Also, for the inter-rater reliability the kappa index remained consistent between the two dates of reading. This shows that our calibration was consistent between the two dates.

Agreement between skeletal maturation indicators

CVM vs. Hand-Wrist Maturation

In previous studies between hand-wrist and cervical vertebrae maturation, there is great variability in the agreement between the two indices. In Hoseini's study, the average kappa index between the two indicators was calculated to be 0.312. The kappa index was 0.27 among the 66 girls and 0.33 among the 67 boys in their study, which indicates fair agreement and slightly higher concordance in boys between the two methods (Hoseini et al. 2016). The agreement was much higher in studies by Uysal et al. (Pearson coefficient (r) = 0.78 for boys; r = 0.88 for girls) (Uysal et al. 2006), Pichai et al. (κ = 0.60; r=0.945) (Pichai et al. 2014) and Gandini et al (κ = 0.786) (Gandini, Mancini, and Andreani 2006). It is important to note that some of the variability between studies could be due to the difference in sample sizes and the variety of cervical vertebrae maturation and hand-wrist methods used. Also, when performing comparison, it is critical to distinguish between the statistical measures used, it is not appropriate to directly compare Pearson's correlation coefficient to kappa.

In our study the kappa agreement was 0.4563; and the Pearson correlation coefficient (r) was 0.68456. These indicate moderate agreement between hand-wrist and cervical vertebrae maturation. Our numbers are comparable to previous studies, indicating these two maturation indices are correlated but not interchangeable. Looking at table 11, which shows the frequency distribution of hand-wrist to CVM, it can be concluded that the hand-wrist develops slightly earlier than CVM. In patient's that have a completely fused middle phalanx, their CVM could still be considered a stage 2 or 3 and still has several stages of maturation remaining.

CVM vs. Spheno-occipital Synchondrosis

The study by Fernandez-Perez found a strong correlation between cervical vertebrae maturation and spheno-occipital synchondrosis closure indicators with the Pearson correlation coefficient of 0.89 (Fernandez-Perez et al. 2016). The Demirturk study concluded that cervical vertebrae maturation and spheno-occipital synchondrosis closure were very strongly correlated in men (r=0.851) and strong in females (r=0.618) (Demirturk Kocasarac et al. 2017).

Since both of these studies used the Pearson correlation coefficient, we also calculated Pearson correlation coefficient. However, this is typically a statistical test reserved for continuous data and our data is ordinal. For our study the Pearson coefficient was 0.68456, which is indicative of moderate correlation and the kappa was 0.2511, which indicates fair agreement. This correlation is slightly lower than the previous studies that have related the cervical vertebrae maturation to the spheno-occipital synchondrosis closure. The kappa statistic for this comparison is not considered statistically significant and therefore could have occurred by chance. When looking at table 12, which shows the frequency between spheno-occipital synchondrosis and cervical vertebrae maturation, spheno-occipital synchondrosis tends to cluster at later stages, while CVM is spread out but focuses on earlier stages. In our study there are few subjects less than age 11.5, but many subjects have CVM in early stages. Conversely, not many subjects were over 14.5 years old but many had spheno-occipital synchondroses in the later stages of development. This indicates that stages of CVM start to develop later than the spheno-occipital synchondrosis stages.

Hand-wrist vs. Spheno-occipital synchondrosis

The only published study that shows the agreement between hand-wrist maturation and spheno-occipital synchondrosis closure was a thesis by Hight (Hight 1980). This study is not a good comparison to our study because the methods were very different. It focused on the adductor sesamoid, rather than the third phalanx and used midsagittal cephalometric laminagraph, whereas ours used CBCT images. Therefore, when looking at the comparison it is important to keep in mind the different methods that were used. Hight concluded that the adductor sesamoid development was shown to be closely related to spheno-occipital synchondrosis development ($r = 0.82$, female; $r = 0.77$ male).

Our correlation coefficient was slightly lower than that found in Hight's study, but similar at $r = 0.73655$. The kappa coefficient was 0.5079; this indicates a substantial agreement between the hand-wrist maturation and spheno-occipital synchondrosis maturation. The table 13 that displays the frequency between the two indicators shows that the hand-wrist and spheno-occipital synchondrosis visually correlate better to each other than to CVM. The stages tend to have a similar pattern of distribution.

Summary of Agreement for Five Stage Analysis

In our study, the two maturation indicators that had the highest agreement were hand-wrist to spheno-occipital synchondrosis ($\kappa = 0.5079$), followed by cervical vertebrae maturation to hand-wrist maturation (κ = 0.4563) and lastly cervical vertebrae to spheno-occipital synchondrosis (κ = 0. 2511) showed the lowest agreement. In fact, for the comparison of the cervical vertebrae maturation to the spheno-occipital synchondrosis closure, only one of the rater's agreements was statistically significant, and the consensus was not statistically significant. The cervical vertebrae maturation is the skeletal maturation indicator that has the least correlation to the other two indicators.

Pre-peak, peak and post-peak growth status agreement

It is most important for a clinician to be able to look at a radiograph and assess how much growth potential a patient has, rather than to determine their exact numerical stage of maturation. Therefore, the five stages for each maturation indicator were grouped into three clinical categories: pre-peak growth, peak growth and post-peak growth. For the comparison of cervical vertebrae maturation to hand-wrist maturation, the kappa statistic was 0.5421, indicating moderate agreement using the three-stage system. Comparing cervical vertebrae maturation to spheno-occipital synchondrosis closure, the kappa statistic was 0.3177, indicating just fair agreement using the three-stage system. Lastly, the kappa statistic was 0.5492 indicating moderate agreement between the spheno-occipital synchondrosis closure and hand-wrist maturation. The agreements between CVM to hand-wrist and hand-wrist to spheno-occipital synchondrosis were comparable and statistically significant, while the agreement of CVM to spheno-occipital synchondrosis was less and not statistically significant.

Summary of Age Statistics

Regardless of the correlation to each other, skeletal growth or facial growth, it is widely accepted that each of the skeletal maturation indicators will be correlated to an increase in age as the stage increases. Our data showed that for both hand-wrist and cervical vertebrae, the mean age for each stage of maturation does increase, however for the spheno-occipital synchondrosis the age increase is not as clear or consistent. For example, the mean age for stage 2 was lower than that for stage 1. For the stages 1-3 of the spheno-occipital synchondrosis, the mean ages are comparable. One explanation for this is that when viewing the spheno-occipital synchondrosis on a CBCT, since it is a full head scan with lower resolution, small areas of calcification can be missed, or multiple smaller areas of calcification could be mistaken for one.

The summary statistics for age were also done for the stages of pre, peak and post pubertal growth. This did show an increase in mean age for each maturation indicator, however it was still not considered statistically significant for the spheno-occipital synchondrosis closure. According to this summary, the average age of peak growth when observing the cervical vertebrae is 13.33 years old. This is slightly older than the average age for peak growth according to both the hand wrist maturation and spheno-occipital synchondrosis closure, which was 12.95 and 12.71 years of age respectively. This agrees with what we discussed earlier in our study – that the CVM matures later than both the spheno-occipital synchondrosis and hand-wrist. Another conclusion that can be drawn from table 15 is that if we see post-peak growth of the spheno-occipital synchondrosis, meaning the synchondrosis is close to complete fusion or completely fused, there may still be growth remaining according to hand-wrist and CVM.

According to hand-wrist maturation, in our study adolescents achieve peak growth at age 12.95. This age is in between the onset of peak height velocity for males and females as established in previous hand-wrist maturation studies (Hagg and Taranger 1982). Our age analysis did account for the difference in age between males and females and showed that the average age for peak growth in females was 12.4 years old and for males it was 13.42 years old. There is approximately 1-year difference in between peak growth ages for males and females in our study, whereas previous studies have suggested a two year difference (Hagg and Taranger 1982). This could be due to the limited number of subjects in our study.

In a study that examined the spheno-occipital synchondrosis on CBCTs, they determined the spheno-occipital synchondrosis was closed by age 13 (Okamoto et al. 1996), this coincides with our data that suggested post-peak mean age as determined by the spheno-occipital synchondrosis was at 13.77 years old.

The distribution of males and females between each of the stages for the cervical vertebrae and hand-wrist are relatively equal, but for the spheno-occipital synchondrosis, the females are clustered towards the later stages while the males are clustered towards the earlier stages. In fact, there were no females that were graded having a completely patent spheno-occipital suture. For all three skeletal maturation indicators, the average age at each stage is younger for females than for males. This agrees with many previous studies that females mature earlier than males.

Agreement of all three maturation indicators

Graphs were used as a visual way to assess the agreement between the three maturation indicators at once. At a CVM stage of 1, most hand wrist stages were pre-pubertal, either a stage 1 or 2 and the spheno-occipital synchondrosis stages are concentrated around stages 2-4. At the CVM stage of 2, both hand-wrist and spheno-occipital synchondrosis stages are wide spread. At the CVM stage of 3, both the hand-wrist and spheno-occipital synchondrosis stages are concentrated around stages 4 and 5. Therefore, this indicates that at what is considered peak growth stage of CVM, the hand-wrist and spheno-occipital synchondrosis appear further along in their maturation. At CVM stage 4, the majority of hand-wrist and spheno-occipital synchondrosis stages are from 3-5. Lastly, at CVM stage 5, the majority of hand-wrist and spheno-occipital stages are either 4 or 5, indicating post-pubertal growth.

It is interesting that when comparing age to the skeletal maturation, the mean peak growth for CVM occurs at a younger age than for hand-wrist and spheno-occipital synchondrosis. However, when visually looking at the graphs comparing the three indicators at once, at peak growth stage 3, both hand-wrist and spheno-occipital synchondrosis are further along in their maturation. There are several explanations for this. First, since there is no accurate numerical statistic to measure the correlation between the three maturation indicators at once, visually assessing the graphs is subjective. Secondly, for spheno-occipital synchondrosis, 80% of the patient's in this study were thought to be in stages three or higher. Therefore, regardless of age, the readers graded the spheno-occipital synchondrosis as further along in development. This could be due to the method of analysis that was used. Since the spheno-occipital synchondrosis was scrolled through in a sagittal manner while grading it, allowing the reader to visualize the entire spheno-occipital synchondrosis, there were more opportunities to see even small areas of fusion, which may not be seen in one stagnant mid-sagittal picture.

Clinical Implications

Both hand-wrist maturation and cervical vertebrae maturation have been used in orthodontics and other fields for decades to determine the skeletal growth potential of patients. Spheno-occipital synchondrosis maturation has been used in areas such as forensic science and anthropology to determine people's age because they had access to skull and histological slices. It is a is a relatively new way for orthodontists to assess what stage of growth a patient is at. With the use of CBCTs, viewing the spheno-occipital synchondrosis is easier than with conventional lateral cephalometric radiographs and therefore it is worthwhile to assess its relationship to other common skeletal maturation indicators.

Our data showed that the three markers studied are not interchangeable and a clinician should evaluate as much data as they have to determine growth potential and to develop a proper diagnosis and treatment plan; one marker alone is not sufficient.

The hand-wrist radiograph is thought to be the gold standard in terms of a reliable skeletal maturation indicator, but in practices that are using only CBCTs, there may not be a cephalometric radiograph machine therefore, taking HW is not readily available. With improvement and clarification of a spheno-occipital synchondrosis closure analysis, it has the potential to become a reliable indicator of growth. The spheno-occipital synchondrosis should be viewed on sagittal and axial slices to best evaluate to best evaluate calcification points.

We found that evaluating CVM is more difficult than evaluating the hand-wrist, so clinicians should put effort into learning the system and its nuances if they are going to use it. When assessing growth of a patient, our data indicates that is it important to keep in mind that the cervical vertebrae may mature later than the spheno-occipital synchondrosis and hand-wrist. Also, CVM does not always elongate fully. A completely grown patient may have a square shaped CVM and no remaining growth potential.

Limitations & Future Studies

While it is helpful to know the relationship between the analyses of the skeletal maturation indicators, it would be more helpful to know the amount of jaw growth associated with each stage of spheno-occipital synchondrosis. Many of the patients in this study had a second CBCT at the end of treatment. Assessing amount of mandibular growth as the spheno-occipital synchondrosis calcification progresses could be a future study.

With more extensive calibration sessions, the inter and intra examiner reliability could be increased, especially for the spheno-occipital synchondrosis. Also, with clarification of the stages of CVM, the reliability could have improved as well. For example, there are situations in which there is a curvature seen at the bottom on the vertebrae, yet the shape as not yet changed. Therefore, it was often hard to decide which stage a patient's vertebrae falls into. Future studies could focus on further calibration and improved definitions of stages for both these skeletal maturation indicators to increase the agreement between examiners.

Future studies could also have a larger sample size to confirm the findings of this study. Other studies had sample sizes of 116-315 subjects (Fernandez-Perez et al. 2016; Demirturk Kocasarac et al. 2017). Also, as seen in Table 1, our patients' ages cluster around 11.5-14 years old, which is to be expected since our subjects were seeking orthodontic treatment. However, if the number of patients were spread out more equally through the age groups, the data would be more encompassing of different stages of maturation.

Conclusions

- The intra-rater and inter-rater agreement was highest for the hand-wrist maturation and lowest for the spheno-occipital synchondrosis closure. All three indices were of substantial or near perfect agreement, indicating that they are reliable.
- The agreement between hand-wrist maturation and spheno-occipital synchondrosis closure was the highest and indicative of moderate agreement. The agreement between hand-wrist and cervical vertebrae was slightly lower, but also indicative of moderate agreement. The agreement between cervical vertebrae maturation and spheno-occipital synchondrosis closure was the lowest; there was only fair agreement and it is not statistically significant. The maturation indices used are correlated, but not interchangeable
- The cervical vertebrae and hand-wrist maturation show a significant correlation with age, whereas the spheno-occipital synchondrosis closure is not well correlated to age.

REFERENCES:

Baccetti, T., L. Franchi, and J. A. McNamara, Jr. 2002. 'An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth', *Angle Orthod*, 72: 316-23.

Baccetti, Tiziano, Lorenzo Franchi, and James A. McNamara. 2005. 'The Cervical Vertebral Maturation (CVM) Method for the Assessment of Optimal Treatment Timing in Dentofacial Orthopedics', *Seminars in Orthodontics*, 11: 119-29.

Bassed, R. B., C. Briggs, and O. H. Drummer. 2010. 'Analysis of time of closure of the spheno-occipital synchondrosis using computed tomography', *Forensic Sci Int*, 200: 161-4.

Bjork, A., and S. Helm. 1967. 'Prediction of the age of maximum puberal growth in body height', *Angle Orthod*, 37: 134-43.

Coben, S. E. 1998. 'The spheno-occipital synchondrosis: the missing link between the profession's concept of craniofacial growth and orthodontic treatment', *Am J Orthod Dentofacial Orthop*, 114: 709-12; discussion 13-4.

Cunha, A. C., L. H. Cevidanes, E. F. Sant'Anna, F. R. Guedes, R. R. Luiz, J. A. McNamara, L. Franchi, and A. C. O. Ruellas. 2018. 'Staging hand-wrist and cervical vertebrae images: a comparison of reproducibility', *Dentomaxillofac Radiol*: 20170301.

Demirturk Kocasarac, H., A. B. Altan, C. Yerlikaya, A. Sinanoglu, and M. Noujeim. 2017. 'Correlation between spheno-occipital synchondrosis, dental age, chronological age and cervical vertebrae maturation in Turkish population: is there a link?', *Acta Odontol Scand*, 75: 79-86.

Enlow, D.H. 1990. *Facial Growth* (W. B. Saunders Company: Philadelphia).

Fernandez-Perez, M. J., J. A. Alarcon, J. A. McNamara, Jr., M. Velasco-Torres, E. Benavides, P. Galindo-Moreno, and A. Catena. 2016. 'Spheno-Occipital Synchondrosis Fusion Correlates with Cervical Vertebrae Maturation', *PLoS One*, 11: e0161104.

Fishman, L. S. 1982. 'Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films', *Angle Orthod*, 52: 88-112.

Flores-Mir, C., B. Nebbe, and P. W. Major. 2004. 'Use of skeletal maturation based on hand-wrist radiographic analysis as a predictor of facial growth: a systematic review', *Angle Orthod*, 74: 118-24.

Franchi, L., T. Baccetti, and J. A. McNamara. 2004. 'Postpubertal assessment of treatment timing for maxillary expansion and protraction therapy followed by fixed appliances', *Am J Orthod Dentofacial Orthop*, 126: 555-68.

Gabriel, D. B., K. A. Southard, F. Qian, S. D. Marshall, R. G. Franciscus, and T. E. Southard. 2009. 'Cervical vertebrae maturation method: poor reproducibility', *Am J Orthod Dentofacial Orthop*, 136: 478 e1-7; discussion 78-80.

Gandini, P., M. Mancini, and F. Andreani. 2006. 'A comparison of hand-wrist bone and cervical vertebral analyses in measuring skeletal maturation', *Angle Orthod*, 76: 984-9.

Greulich, W. W., and S. I. Pyle. 1959. *Radiographic Atlas of Skeletal Development of the Hand and Wrist* (Stanford University Press: Stanford).
Grunheid, T., J. R. Kolbeck Schieck, B. T. Pliska, M. Ahmad, and B. E. Larson. 2012. 'Dosimetry of a cone-beam computed tomography machine compared with a digital x-ray machine in orthodontic imaging', *Am J Orthod Dentofacial Orthop*, 141: 436-43.
Hagg, U., and J. Taranger. 1982. 'Maturation indicators and the pubertal growth spurt', *Am J Orthod*, 82: 299-309.
Hassel, B., and A. G. Farman. 1995. 'Skeletal maturation evaluation using cervical vertebrae', *Am J Orthod Dentofacial Orthop*, 107: 58-66.
Hatcher, D. C. 2010. 'Operational principles for cone-beam computed tomography', *J Am Dent Assoc*, 141 Suppl 3: 3S-6S.
Hight, J.R. 1980. 'The Correlation of Spheno-occipital Synchondrosis FUsion to Hand-Wrist Maturation', University of Tennessee.
Hoseini, M., S. Zamaheni, H. Bashizadeh Fakhar, F. Akbari, J. Chalipa, and A. Rahmati. 2016. 'Comparative Evaluation of the Efficacy of Hand-Wrist and Cervical Vertebrae Radiography for the Determination of Skeletal Age', *Iran J Radiol*, 13: e21695.
Ingervall, B., and B. Thilander. 1972. 'The human spheno-occipital synchondrosis. I. The time of closure appraised macroscopically', *Acta Odontol Scand*, 30: 349-56.
Irwin, G. L. 1960. 'Roentgen determination of the time of closure of the spheno-occipital synchondrosis', *Radiology*, 75: 450-3.
Joshi, V., T. Yamaguchi, Y. Matsuda, N. Kaneko, K. Maki, and T. Okano. 2012. 'Skeletal maturity assessment with the use of cone-beam computerized tomography', *Oral Surg Oral Med Oral Pathol Oral Radiol*, 113: 841-9.
Kinder, M., Theis, D., John, M. T., Ahmad, M. 2009. "Classification of Spheno-Occipital Synchondrosis in Children: A cross-sectional radiographic analysis." In.
Lamparski, D.G. 1972. 'Skeletal age assessment utilizing cervical vertebrae', University of Pittsburgh
Ludlow, J. B., R. Timothy, C. Walker, R. Hunter, E. Benavides, D. B. Samuelson, and M. J. Scheske. 2015. 'Effective dose of dental CBCT-a meta analysis of published data and additional data for nine CBCT units', *Dentomaxillofac Radiol*, 44: 20140197.
Madhu, S., A. M. Hegde, and A. K. Munshi. 2003. 'The developmental stages of the middle phalanx of the third finger (MP3): a sole indicator in assessing the skeletal maturity?', *J Clin Pediatr Dent*, 27: 149-56.
McNamara, J. A., Jr., and L. Franchi. 2018. 'The cervical vertebral maturation method: A user's guide', *Angle Orthod*, 88: 133-43.
Melsen, B. 1972. 'Time and mode of closure of the spheno-occipital synchrondrosis determined on human autopsy material', *Acta Anat (Basel)*, 83: 112-8.
Nestman, T. S., S. D. Marshall, F. Qian, N. Holton, R. G. Franciscus, and T. E. Southard. 2011. 'Cervical vertebrae maturation method morphologic

criteria: poor reproducibility', *Am J Orthod Dentofacial Orthop*, 140: 182-8.
Okamoto, K., J. Ito, S. Tokiguchi, and T. Furusawa. 1996. 'High-resolution CT findings in the development of the sphenooccipital synchondrosis', *AJNR Am J Neuroradiol*, 17: 117-20.
Pichai, S., M. Rajesh, N. Reddy, G. Adusumilli, J. Reddy, and B. Joshi. 2014. 'A comparison of hand wrist bone analysis with two different cervical vertebral analysis in measuring skeletal maturation', *J Int Oral Health*, 6: 36-41.
Powell, T. V., and A. G. Brodie. 1963. 'Closure of the Spheno-Occipital Synchondrosis', *Anat Rec*, 147: 15-23.
Predko-Engel, A., M. Kaminek, K. Langova, P. Kowalski, and P. S. Fudalej. 2015. 'Reliability of the cervical vertebrae maturation (CVM) method', *Bratisl Lek Listy*, 116: 222-6.
Proffit, W.R., H.W. Fields, and D.M. Sarver. 2013. *Contemporary Orthodontics* (Mosby: St.Louis, MO).
Rainey, B. J., G. Burnside, and J. E. Harrison. 2016. 'Reliability of cervical vertebral maturation staging', *Am J Orthod Dentofacial Orthop*, 150: 98-104.
Saito, T. 1989. '[The effects of morphological variation of the spheno-occipital complex to the formation of skeletal facial pattern]', *Nihon Kyosei Shika Gakkai Zasshi*, 48: 226-45.
Santiago, R. C., L. F. de Miranda Costa, R. W. Vitral, M. R. Fraga, A. M. Bolognese, and L. C. Maia. 2012. 'Cervical vertebral maturation as a biologic indicator of skeletal maturity', *Angle Orthod*, 82: 1123-31.
Signorelli, L., R. Patcas, T. Peltomaki, and M. Schatzle. 2016. 'Radiation dose of cone-beam computed tomography compared to conventional radiographs in orthodontics', *J Orofac Orthop*, 77: 9-15.
Soegiharto, B. M., S. J. Cunningham, and D. R. Moles. 2008. 'Skeletal maturation in Indonesian and white children assessed with hand-wrist and cervical vertebrae methods', *Am J Orthod Dentofacial Orthop*, 134: 217-26.
Sohrabi, A., S. Babay Ahari, H. Moslemzadeh, A. Rafighi, and Z. Aghazadeh. 2016. 'The reliability of clinical decisions based on the cervical vertebrae maturation staging method', *Eur J Orthod*, 38: 8-12.
Uysal, T., S. I. Ramoglu, F. A. Basciftci, and Z. Sari. 2006. 'Chronologic age and skeletal maturation of the cervical vertebrae and hand-wrist: is there a relationship?', *Am J Orthod Dentofacial Orthop*, 130: 622-8.
Verma, D., T. Peltomaki, and A. Jager. 2009. 'Reliability of growth prediction with hand-wrist radiographs', *Eur J Orthod*, 31: 438-42.
Viera, A. J., and J. M. Garrett. 2005. 'Understanding interobserver agreement: the kappa statistic', *Fam Med*, 37: 360-3.